

INTERNATIONAL PRELIMINARY EXAMINATION REPORT



(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P20277-PCT		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/GB 03/04351	International filing date (day/month/year) 08.10.2003	Priority date (day/month/year) 08.10.2002	
International Patent Classification (IPC) or both national classification and IPC A61K31/515			
Applicant AMERSHAM PLC et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 11 sheets, including this cover sheet.
 - ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:
 - I ☒ Basis of the opinion
 - II ☐ Priority
 - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain documents cited
 - VII ☐ Certain defects in the international application
 - VIII ☐ Certain observations on the international application

Date of submission of the demand 23.03.2004	Date of completion of this report 26.01.2005
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I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-55 as originally filed

Claims, Numbers

1-32 filed with telefax on 03.11.2004

Drawings, Sheets

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

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5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 30-32 (IA)

because:

☒ the said international application, or the said claims Nos. 30-32 (IA) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	3-8, 10-14, 17, 18, 23-32
	No: Claims	1, 2, 9, 15, 16, 19-22
Inventive step (IS)	Yes: Claims	
	No: Claims	1-32
Industrial applicability (IA)	Yes: Claims	1-29
	No: Claims	

2. Citations and explanations

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see separate sheet

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Re Item I

Basis of the report

Art 34(2)(b) The amendments filed with telefax dated 03.11.2004 do not introduce subject-matter which extends beyond the content of the application as filed. Therefore, the requirements of Article 34(2)(b) PCT are met.
Present claims 1-32 have been examined.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 30-32 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: Biological Chemistry (08-2001), 382(8), 1277-1285
D2: Bioorganic And Medicinal Chemistry Letters (23-04-2001), 11(8), 969-972
D3: Journal Of Nuclear Medicine (1981), 22(6), P12-P13
D4: EP-A-0293971
D5: US-A-3952091
D6: US-A-4124760
D7: WO-A-9960018

If not mentioned otherwise, the relevant passages are those mentioned in the International Search Report.

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Art 33(2) The present application does not meet the requirements of Article 33(2) PCT, since the subject-matter of claims 1, 2, 9, 15, 16 and 19-22 is not new.

D1 discloses MMP inhibiting barbituric acid derivatives. In particular compound 16 (but also compounds 15 and 17-26) is nearly identical with precursor compounds disclosed in the present application (see e.g. present compound 6 or 11). Present claim 19 merely defines a barbituric acid MMP inhibitor being conjugated to a ligand which is capable of forming a metal complex. Consequently, the metal complex is not a distinguishing feature. The desideratum definition of the ligand "forming a metal complex ... which is resistant to transchelation" is not suitable to render present claims 19-22 novel over D1.

However, D1 does not mention the feature "sterile form" of present claim 26 which corresponds to original claim 24.

In summary, the subject-matter of claims 19-22 is not new in the light of D1.

D2 discloses barbituric acid derivatives being substituted at the 5 position by a ligand which is capable of a reaction with radioactive non-metal. For the same reasons as mentioned above, the subject-matter of present claims 19-22 is not new in the light of D2.

D3 discloses barbituric acid derivatives having an imaging moiety (radioactive non metal) linked to position 5 of the barbituric acid. As selenium and tellurium isotopes are gamma radiation emitting non-metals, the IPEA agrees that the disclosure of D3 does not fall within the scope of present claim 1 or 26. Therefore, the disclosure of D3 is not novelty-destroying for the claims of the present application.

D4 discloses Tritium-labelled phenobarbital which is capable of a reaction with radioactive non-metal. The applicant alleges that "tritium is not an imaging moiety suitable for detection following administration *in vivo*". Examiner stress that the European Pharmacopoeia (2002), lists tritium labelled water for intravenous administration (determination of body water which is *in vivo* detection). In consequence the objection made by the examiner in the Written Opinion is upheld. Therefore, the subject-matter of claims 1, 2, 9, 15 and 16 is

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not considered to be new in the light of D4.

Art 33(3) The present application does not meet the requirements of Article 33(3) PCT, since the subject-matter of claims 1-32 does not seem to involve an inventive step.

D7 discloses the concept of using an imaging moiety containing ligands of the present invention bound to different biologically active compounds in the manufacture of radiopharmaceuticals. The thus obtained radiopharmaceuticals are *inter alia* useful in the diagnosis of atherosclerosis. Consequently, D7 discloses the concept of targeting imaging moieties. Therefore it is still considered to be appropriate to start the problem solution approach from D7. The problem to be solved by the present invention may therefore be regarded as how to provide improved radiopharmaceuticals for the use in the diagnosis of atherosclerosis.

The present application suggests to solve the problem posed by providing barbituric acid being substituted at the 5 position by a ligand that comprises a imaging moiety or by a ligand which is capable of a reaction with radioactive non-metal or which is capable of forming a complex with a radioactive or paramagnetic metal.

D1 and D2 disclose the MMP binding properties of barbituric acids. The overexpression of MMPs in atherosclerotic plaques was known at the priority date of the present application (see description page 2, lines 25-30)

Taking into account the teaching of the cited prior art the following reasoning applies:

With respect to the subject-matter of claims 1, 2, 9, 15, 16 and 19-22 the applicant's attention is drawn to the fact that even if novelty could be established over the above-cited prior art it is at present not clear wherein an inventive step may reside.

With respect to the subject-matter of the remaining claims 3-8, 10-14, 17, 18 and 23-32 the applicant's attention is drawn to the fact that there seems to be no basis for inventive step within the present application as filed since no evidence can be found that the features which are novel result in a solution of the posed problem which could not have been foreseen by the skilled person. Being aware of the fact that MMPs are a potential target for

radiopharmaceuticals useful in the diagnosis of atherosclerosis the skilled man performed an arbitrary choice out of one list containing all known MMP inhibitors to select barbituric acid derivatives. The structural features of the ligands and radioactive compounds has been anticipated by D7.

It is therefore noted, that the solution proposed in claims of the present application is not considered to be inventive in the sense of Article 33(3) PCT.

But even when starting from D3 as the applicant suggests claims 1-18 and 23-32 do not seem to involve an inventive step. D3 discloses the use of radioactive gamma-emitting non-metals being conjugated to barbituric acids as *in vivo* diagnostics. The subject-matter differs from that of the present application in that D3 does not use imaging moieties which are chosen from items (i)-(vii) as defined by present claim 1.

The problem to be solved could - again - be regarded as how to provide improved radiopharmaceuticals for the use in the diagnosis of atherosclerosis. The present application suggests to solve the problem by using imaging moieties as defined by present claim 1.

This solution is not considered to be inventive as no evidence can be found that the features which are novel result in a solution of the posed problem which could not have been foreseen by the skilled person. the use of imaging moieties as defined by present claim 1 are well-known in the field of

radiopharmaceuticals. Since there is no surprising effect resulting from that choice the solution as suggested by the present application cannot be considered as being inventive.

Art 33(4) For the assessment of the present claims 30-32 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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The subject-matter of claims 1-29 is considered to be industrially applicable in the sense of Art 33(4) PCT.